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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/553,995 | 06/20/2006 | Robert Francis Grimble | BJS-620-397 | 6576 |

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| EXAMINER | |
|---|---|
| STRZELECKA, TERESA E | |
| ART UNIT | PAPER NUMBER |
| 1637 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/553,995 | GRIMBLE ET AL. | |
| | Examiner | Art Unit | |
| | TERESA E. STRZELECKA | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/20/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

## DETAILED ACTION

1. Claims 1-10 are pending in the instant application and will be examined.

### *Information Disclosure Statement*

2. The information disclosure statement (IDS) submitted on October 20, 2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

### *Sequence Rules Compliance*

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

APPLICANT IS GIVEN time of response to this office action WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

The sequence listing filed with the application does not contain a statement that the paper and electronic copies are the same.

***Claim Interpretation***

4. Applicants defined the term "fish oil" on page 21, lines 1-4, as follows:

"For the purposes of the present invention, fish oil is oil extracted from the flesh and organs of fish which contains at least 28% n-3 PUFAs, of which about 60% is eicosapentaenoic acid and about 40% is docosahexaenoic acid."

5. Applicants defined the term "treatment" on page 22, lines 1—23, as follows:

"The term "treatment" as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g. in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the inflammatory condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the inflammatory condition, and cure of the inflammatory condition. Treatment as a prophylactic measure (i.e. prophylaxis) is also included."

Therefore, the term "treatment" encompasses cure and prevention.

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of assessing the susceptibility of a healthy individual to treatment with fish oil, where the treatment does not incorporate cure or prophylaxis, does not reasonably provide enablement for the claimed method of assessing the susceptibility of an individual suffering from inflammatory disease to treatment with fish oil and method of treatment of an individual affected with inflammatory disease with fish oil, where the treatment includes cure and prophylaxis.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-7 are broadly drawn to a method of assessing the susceptibility of an individual to treatment of an inflammatory disease with fish oil, comprising determining the genotype of the individual in relation to polymorphisms at the TNF-α -308, LT-α +252 and/or IL-6 -174 alleles; and inferring therefrom whether said individual responds well to treatment with fish oil. Claims 8-10 are drawn to a method of treatment of an inflammatory disease in a patient, which comprises assessing the susceptibility of an individual to treatment of an inflammatory disease with fish oil, said assessment comprising: a) determining the genotype of the individual in relation to polymorphisms at the TNF–α-308, LT-α +252 and/or IL-6 -174 alleles; and b) inferring therefrom whether said individual responds well to treatment with fish oil; and treating said individual with an appropriate amount of fish oil. However, as will be further discussed, there is no support in the specification and prior art for the in vivo methods, only for ex vivo or in vitro methods. The invention is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Working Examples

The specification has no working examples of assessing the susceptibility of individuals suffering from inflammatory disease of any type to fish oil treatment based on the genotype of TNF−α-308, LT-α +252 and/or IL-6 -174 alleles. In fact, smokers and individuals with inflammatory disease were specifically excluded from the study.

Guidance in the Specification.

The specification provides no evidence that the disclosed correlation between certain TNF−α-308, LT-α +252 and/or IL-6 -174 alleles and the response to fish oil in terms of TNF-α production can be extended to individuals already suffering from inflammatory disease. Further, as the term "inflammatory disease" encompasses thousands of possible diseases and disorders, none of which were investigated with respect to response to fish oil and reduction of TNF-α production, the guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed methods to use the claimed invention. The specification merely discloses that healthy individuals with certain genotypes of TNF−α-308, LT-α +252 and/or IL-6 -174 respond better to fish oil in terms of the decrease in TNF-α production. As the levels of these inflammatory cytokines are increased to different degrees in individuals suffering from inflammatory disease, investigation of the effects if healthy individuals is not predictive of the response exhibited in patients suffering from inflammatory diseases.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

The unpredictability of the art and the state of the prior art

Analysis of the most recent literature with respect to some of the inflammatory diseases, the role of cytokines and the possible use of fish oil show that in 2008, five years after the filing date of the priority application for this case, there is no cure for any of the inflammatory disorders, and that the role played by fish oil in treatment of the inflammatory diseases needs to be further investigated.

Williams et al. (Curr. Opinion Pharmacol., vol. 7, pp. 412-417, 2007) reviewed use of cytokine inhibitors, especially TNF-α inhibitors, in such diseases as rheumatoid arthritis (RA), Crohn's disease (CD), ankylosing spondylytis (AS) and psoriasis. The concluded the following (Abstract):

"TNFα blockade, however, is a treatment, rather than a cure, and is not effective in all patients or in all autoimmune diseases and further research is needed to get closer to a cure."

Williams et al. point to the fact that blocking TNFα blockade decreasesd severity of RA symptoms, but did not alleviate the disease in at least 25% of patients (page 413, first paragraph; Table 1).

In a very recent paper Scheinecker et al. (Immunity, vol. 28, pp. 440-444, April 2008) reviwed anti-cytokine treatments in inflammatory diseases (page 440, first and second paragraphs). They teach that TNFα or IL-6 blocking treatments provide relief from symptoms of RA, AS, psoriasis and CD, but so far there is no cure for any of these diseases (page 440, fourth paragraph; page 441, second paragraph; page 442, fourth paragraph). Scheinecker et al. conclude with the following (page 442, last paragraph; page 443, first paragraph):

"Currently, we can achieve stringent remissions, i.e., no evidence of active disease, with consequential therapy in about 20% of the patients in clinical practice. However, cure is not yet in sight. Although cure will ultimately require knowing the cause or causes of these disorders, it is conceivable that interference with the vicious cycle of the inflammatory occurrences very early in the course of the disease process may reverse the events usually destined to become chronic in predisposed individuals. Such window of opportunity is addressed by currently ongoing clinical trials, and it remains to be seen if this hypothesis can come true.", and (page 443, last paragraph):

In summary, targeting of proinflammatory cytokines such as TNF or IL-6 is highly efficacious in rheumatoid arthritis and, at least for anti-TNF agents, also other chronic inflammatory rheumatic and nonrheumatic inflammatory disorders. They substantially improve signs and symptoms and retard or prevent organ damage and disability, the most devastating consequence of these chronic conditions. Although the progress made over the past dozen or so years has dramatically improved the fate of the patients, we still lack sufficient predictive insights to determine the optimal therapeutic strategy for the individual patient. Moreover, despite all these advances, the overall rate of good responses is limited, with only about 10%–40% of patients achieving improvement of 70%or more with any one of these agents based on clinical scoring. Thus, although with increasing therapeutic options an increasing number of patients will achieve a good clinical result and, ideally, remission, new compounds with even better efficacy and better safety will still be needed. In parallel, the search for causes, the search for predictors, and the search for explanations of the effects of many of these therapies will have to go on."

In conclusion, both of these references point to the fact that a lot of research is still necessary to determine the causes of inflammatory diseases in order to find better therapies, and, ultimately, the cure. Also, since the causes of these diseases are not known, prophylaxis is not possible.

Finally, in a review devoted to the role of n-3 polyunsaturated fatty acids in inflammatory diseases, Calder (Am. J. Clin. Nutr., vol. 83 (suppl), pp. 1505S-1519S, 2006) teaches that studies of the effect of fish oil on the levels of inflammatory cytokines in humans yielded contradictory results (page 1510S, second paragraph). In terms of particular diseases, fish oil was shown to decrease the severity of symptoms in RA patients (page 1511S, third and fifth paragraphs; page 1512S, first paragraph). However, the benefits for patients with inflammatory bowel diseases were not very

clearly defined in view of a meta-analysis of several clinical trials (page 1513S, third and fourth paragraph; page 1514S, first and second paragraph). Calder concludes with the following (page 1515S, last paragraph):

"Evidence of the clinical efficacy of long-chain n-3 PUFAs is strong in some settings (eg, in rheumatoid arthritis) but is weak in others (eg, in inflammatory bowel diseases and asthma). More, better designed, and larger trials are required in inflammatory diseases to assess the therapeutic potential of long-chain n-3 PUFAs. The precursor n-3 PUFA α-linolenic acid does not appear to exert antiinflammatory effects at achievable intakes. The antiinflammatory efficacy of n-3 PUFAs may be improved if intakes of n-6 PUFAs, especially arachidonic acid, are decreased."

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this method to determine whether a patient with a particular inflammatory disease will respond to treatment with fish oil. First, patients with all potential inflammatory diseases in different stages would need to be examined for polymorphisms in TNF-α -308, LT- α +252 and IL-6 -174. Then all of these patients would need to be treated with fish oil under controlled conditions for prolonged periods of time to determine the effects of treatment. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the effects of fish oil in patients with inflammatory diseases depend upon numerous known and unknown parameters, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of fish oil in the treatment of inflammatory diseases. Thus given the broad claims in an art

whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-10 are indefinite in claims 1, 7 and 8. The claims are indefinite over the recitation of "polymorphisms at the TNF-α -308, LT- α +252 and/or IL-6 -174 alleles". It is not clear how many polymorphisms need to be determined, i.e., whether only TNF-α -308 and/or IL-6 -174, only LT- α +252 and/or IL-6 -174, or both TNF-α -308 and LT- α +252 and/or IL-6 -174.

10. No claims are allowed.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
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Primary Examiner, Art Unit 1637
April 30, 2008